SEHSC
SILICONES ENVIRONMENTAL, HEALTH AND SAFETY COUNCIL
NORTH AMERICA

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October 13, 2004

8EHQ-1004-15756

CONTAINS NO CBI

TSCA Document Control Center (7407)
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Attn: TSCA Section 8(e) Coordinator
Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Re: TSCA Section 8(e) Notification of Substantial Risk: A Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Methyltrimethoxysilane in Sprague-Dawley Rats

Dear TSCA Section 8(e) Coordinator:

In accordance with the provisions of Section 8(e) of the Toxic Substances and Control Act (TSCA), as interpreted in the Statement of Interpretation and Enforcement Policy (68 Fed. Reg. 33129; June 3, 2003) and other Agency guidance, the Silicones Environmental, Health and Safety Council (SEHSC), on behalf of its member companies, submits the following information as a TSCA Section 8(e) notification. Neither SEHSC nor any member company has made a determination at this time that any significant risk of injury to human health or the environment is presented by these findings.

SEHSC is a not-for-profit trade association whose mission is to promote the safe use and stewardship of silicones. The Council is comprised of North American silicone chemical producers and importers. SEHSC's members include: Clariant LSM (Florida), Inc.; Dow Corning Corporation; General Electric Silicones; Rhodia Inc.; Shin-Etsu Silicones of America; and Wacker Silicones, A Division of Wacker Chemical Corporation.

Chemical Substance

1185-55-3 Methyltrimethoxysilane

8EHQ-04-15756

Ongoing Study

A Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Methyltrimethoxysilane in Sprague-Dawley Rats – Dow Corning Corporation Study Number: 9896-102.

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MR 280107

Summary

Preliminary results from an ongoing study with Methyltrimethoxysilane show indications of treatment-related effects on organ weight (liver, thymus), tissue morphology (or histopathology) (intestinal mucosa, liver, thyroid, adrenal gland, red blood cells), and clinical pathology parameters (prothrombin time, serum cholesterol and total protein levels, platelet concentration).

Details

Study Design

The objective of this study was to evaluate the potential toxicity of methyltrimethoxysilane (MTMS) in a combined repeated-dose toxicity study that included reproductive/developmental toxicity screening in Sprague-Dawley rats following enhanced test guidelines (Organisation for Economic Co-Operation and Development (OECD) Test Guideline number: 422, (1996) and United States Environmental Protection Agency (U.S.E.P.A.) Health Effects Test Guideline Office of Prevention, Pesticides, and Toxic Substances (OPPTS) 870.3650 (2000)). Dose levels were 0 (control), 50, 250, and 1000 mg MTMS/kg rat. Methyltrimethoxysilane, dissolved in corn oil, was administered by oral gavage once each day for up to 51 consecutive days. Females in each dose level were divided into a toxicity group (10 animals/group) and a reproductive group (10 animals/group). A single group of males (10 animals/dose level) was used for both the toxicity and reproductive phases of the study. Toxicity group females were treated for 28 days. Males were treated for 14 days prior to the mating period, during the mating period, and after the mating period for a total exposure duration of 29 days. Reproductive group females were treated for 14 days prior to the mating period, during the mating period, and then up to and including post-partum day 3.

Preliminary Results

Mucosal Lipidosis

Mucosal lipidosis in the duodenum and/or jejunum was present in 8 of the 10 males in the 1000 mg/kg/day dose group. Both the duodenum and jejunum were affected in 3 of the males, only the duodenum was affected in 1 male, and only the jejunum in 4 others. One male each in the 50 and 250 mg/kg/day dose groups had mucosal lipidosis in the duodenum.

Mucosal lipidosis of the duodenum and/or jejunum was diagnosed in 6 of the 10 females in the 1000 mg/kg/day dose group. Both the duodenum and jejunum were affected in 4 of the females, only the duodenum was affected in one female and only the jejunum in one other.

Liver Organ Weight Increase and Histopathology

Liver weight was increased 20% and 33% in the 250 and 1000 mg/kg/day dose group males, respectively. Diffuse hepatocellular hypertrophy was present in 100% of the 1000 mg/kg/day dose group males and not present in males from any other dose group. Centrilobular hepatocellular hypertrophy was diagnosed in two 250 mg/kg/day dose group males.

Liver weight was increased 37% and 97% in 250 and 1000 mg/kg/day dose group females, respectively. Centrilobular hepatocellular hyperplasia/hypertrophy was present in 50% and 100% of the 250 and 1000 mg/kg/day dose group females, respectively. Periportal vacuolation was present in all dose groups however an increase in incidence/severity grade was limited to the 250 and 1000 mg/kg/day dose groups.

Thyroid Histopathology

Follicular cell hyperplasia/hypertrophy was present in 60% of the 250 mg/kg/day dose group males and in all of the males at 1000 mg/kg/day. This finding was absent in the other dose groups. Severity grade increased with dose.

Follicular cell hyperplasia/hypertrophy was present in all females at the 250 and 1000 mg/kg/day dose groups. This finding was absent in the other dose groups. Severity grade increased with dose.

Thymus Weight Decrease

Thymus weight decreased in a dose-related manner for males. The decreases were 10%, 28%, and 35% for 50, 250, and 1000 mg/kg/day dose group males, respectively. The decreases at 250 and 1000 mg/kg/day were statistically significant. Thymus histopathology was unremarkable.

Females were unaffected.

Adrenal Gland Histopathology

The incidence of adrenal gland cortex hyperplasia/hypertrophy, apoptosis, and lymphocytic infiltration in the zona reticularis were statistically significantly elevated for females in the 1000 mg/kg/day dose group.

Males were unaffected.

Red Blood Cell Morphology

Acanthocytes (spiculated erythrocytes) were detected in treated but not control males and females. The incidence in males was 20%, 10%, and 50% for dose levels of 50, 250, and 1000 mg/kg/day, respectively. Statistical significance was achieved only at the high dose.

The incidence in treated females was 25%, 30%, and 40% for dose levels of 50, 250, and 1000 mg/kg/day, respectively. Statistical significance was achieved only at the high dose.

Increased Prothrombin Time

Prothrombin time for males was 17, 16, 29, and 33 seconds for the control, 50, 250, and 1000 mg/kg/day dose groups, respectively. Prothrombin time prolongation in the 250 and 1000 mg/kg/day dose groups was statistically significant.

Prothrombin time in treated females was not different from control.

Notable Clinical Pathology Findings

Blood platelet concentrations were elevated in both males (16%) and females (20%) in the 1000 mg/kg/day dose groups.

Serum total cholesterol was elevated in 250 and 1000 mg/kg/day dose group females by 30% and 130%, respectively. Males were not similarly affected.

Serum total protein (non-albumin) was elevated in 1000 mg/kg/day dose group males (8%) and in 250 (8%) and 1000 mg/kg/day dose group females (17%).

There were no effects on any reproductive, motor activity, or functional observational battery parameters representative of a treatment-related effect.

Actions

SEHSC will notify EPA of any further relevant information that may be developed concerning this material. SEHSC also will provide EPA with the copy of the final report containing these study results when it is available. If you have any questions concerning this study, please contact me at (703) 904-4322, rmenning@sehsc.com, or at the address provided herein.

Sincerely,

Reo Menning
Executive Director

SEHSC
Silicones Environmental, Health and Safety Council of North America
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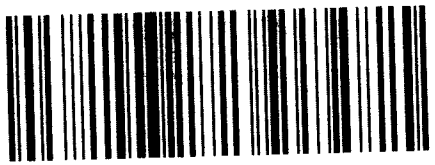

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